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Brain Research 905 (2001) 26–33

BRAIN RESEARCH

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Research report

Agonistic behavior in groups of limbic epileptic male rats: pattern of brain damage and moderating effects from normal rats

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Accepted 20 March 2001

Abstract

Different ratios of normal male rats and male rats in which limbic seizures had been induced by a single systemic injection of lithium and pilocarpine were housed in groups of six. The group ratios ranged along the continuum from all normal rats to all experimental rats. The average numbers of episodes of boxing, biting and mounting–thrusting per rat per hour per group were recorded by direct observation (red light) for 1 h during the midscotophase. Groups that contained less than two normal rats exhibited significantly elevated amounts of agonistic (boxing, biting) behavior but not mounting behavior. Multiple regression analyses showed that combinations of neuronal loss within only two to three areas accommodated at least 50% of the variance in the numbers of these behaviors. © 2001 Elsevier Science B.V. All rights reserved.

Theme: Neural basis of behaviour

Topic: Neuroethology

Keywords: Aggression; Social factor; Groups; Seizure; Brain injury; Rat; Biting; Boxing

1. Introduction

Behaviors that emerge within aggregates of animals should be strongly influenced by the composition of the group. As the numbers (n) of elements (rats) with specific characteristics increase one would expect other n-dependent processes, analogous to a 'critical mass', to emerge. This experiment was designed to discern if there was a linear relationship between the amount of agonistic behavior in groups ($n=6$) of male rats that were normal or more aggressive due to an experimental manipulation.

We found that aggression between cage mates (usually three rats per cage) occurred in rats in which seizures and status epilepticus were induced by a single systemic injection of lithium (3 mEq/kg) and pilocarpine (30 mg/kg). The agonistic behaviors emerged about 15–20 days [1,6,12] after the induction of the seizures when the rats appeared to have 'recovered'. These episodes of aggressive behavior, defined as several minutes of maintaining boxing stances and intermittent biting, were not temporally contiguous with the display of overt spontaneous seizures. These episodes of agonistic behaviors occurred during the scotophase as well as the photophase, when most normal rats are inactive.

When these experimental rats were housed in groups of four in larger cages for several weeks the rats displayed either: (1) phasic aggression during which time they had to be monitored to prevent injury, (2) persistent sexual activity, defined as mounting (of other male rats), pelvic thrusting and genital licking [11], or (3) daily, non-periodic alterations between intragroup agonistic behavior and mounting behaviors. The agonistic behavior has been attenuated [1] to normal levels for triads of male rats exposed to each other for only 1 h per day in small cages or for groups of four rats housed chronically in larger cages by the addition of prednisolone to the water supply (0.25–0.5 mg/cc).

Our behavioral observations suggested that episodes of agonistic behavior within these groups of rats were often associated with a specific 'ear twitching'. This fine, rapid

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PII: S0006-8993(01)02454-4

movement of the pinnae occurred for tens of seconds in rats with the seizure history and appeared to be associated with the amount of damage in the suprageniculate nucleus. Because a bout of agonistic group behavior usually started with two rats and then escalated to involve the entire group, we designed this experiment to discern if the specific ratio of normal to experimental rats that triggered the maximum amount of the more aggressive contacts, specifically biting, was linear or all-or-none.

2. Methods and materials

In 14 separate blocks (six rats/block), a total of 84, 100-day-old male Wistar rats (Charles River, Hull, Quebec) were selected for this study. They had been habituated to colony conditions for at least 2 weeks.

The experimental treatment was the subcutaneous injection of lithium chloride (3 mEq/kg; 1 cc/kg) followed 4 h later by 30 mg/kg of pilocarpine (1 cc/kg). (The neuronal loss induced by this combination is very similar to that induced by a single dosage of 380 mg/kg of pilocarpine [3].) About 30 min after the onset of the overt seizures, defined as rearing, rapid forelimb clonus and falling, and, the subsequent emergence of status epilepticus each rat received 25 mg/kg of acepromazine (Atravet) subcutaneously to facilitate survival. All rats remained in their home cages (groups of three rats/cage) for 10 days.

We have found that all rats that display these behaviors exhibit the conspicuous, multifocal brain damage [9,12]. With this particular dosage of lithium and pilocarpine failure to exhibit this stereotyped sequence of symptoms after systemic injection is very infrequent for male rats in this age range. Both our direct electroencephalographic measurements as well as those reported by others have demonstrated: (1) specific epileptic activity that occurred during the display of the symptoms, and, (2) different types of epileptic patterns were associated with specific types and locations of brain damage [9]. When lower concentrations of these compounds are employed, fewer rats display these symptoms and these rats have never exhibited any neuronal injury discernable by light microscopy [13].

After the protocol had been approved by the Animal Care Committee, the experiment was initiated. In each block, groups of six rats were housed in one of two 140×37×37-cm plastic cages that contained 1/4 inch corncob bedding. The compositions of the groups were: all controls, five controls: one experimental, four controls: two experimentals, an equal number of controls and experimentals, two controls and four experimentals, one control and five experimentals and all experimentals. There were two blocks per composition.

Ten days after each group of rats was assembled (20 days after the induction of the seizures), they were observed under red light (overhead fluorescent) conditions for ten successive nights, between 22:00 h and midnight, for 1 h. During this time the numbers of: (1) boxing episodes, defined as an upright stance and facial opposition to another rat but without biting, (2) bites or attacks, defined as a direct dental contact of one rat with another, and (3) mounts and repeated, pelvic thrusts, which were indiscriminable from the normal copulatory behavior with female rats, were recorded for each rat.

The (average) mean numbers of episodes of boxing, bites and mounts/pelvic thrusts per hour for the ten nights were computed for each rat. The averages of all six rats per cage constituted the values of the behaviors for the different groups (compositions). The temperature in the room in which the cages were housed was controlled and ranged between 19 and 21°C. The photoperiod was 12-h light/dark with the dark cycle beginning at 20:00 h. Food and water were always available ad libitum. The bedding was refreshed once every 5 or 6 days.

Because the observational blocks (case) was the group of rats the sample size for this experiment was 14 (cages, i.e. 14×6 rats=84 rats). One way analysis of variance as a function of the composition of the group was completed for the average numbers of bites, boxing episodes and mounts during the 10-day periods of observation. To discern if the controls and the experimental rats differentially responded to the group composition, the mean values for the controls only or the experimentals only for the three behavioral measures were also analyzed as a function of the group composition. All analyses involved SPSS software. Qualitative patterns were determined by observation and were extracted after the completion of the experiments.

Within about 1 week after the completion of each experiment two rats in which the seizures had been induced were randomly selected from nine of the groups (total $n=18$) that contained between two and six seized rats. The brains were removed, fixed in ethanol–formalin–acetic acid, and processed [10]. Ten micrometer coronal sections were obtained every 100 μm between the posterior and anterior commissures and stained with toluidine blue O. This area contains all of the structures that are discernably damaged by the seizures induced by the lithium and pilocarpine [3,9]. The combination of this specific fixative and stain reveals clear cellular detail at both 200× and 400× and minimal processing artifacts such as cracks or fragmentation of the ribbons.

The proportion of damage within all of the Paxinos and Watson [8] structures that are contained within the boundary of the two commissures were discerned by dividing the number of sections that contained conspicuous evidence of damage within a structure by the total number of sections examined for that structure [12]. The determination of damage was defined primarily by the discriminable reduction in the numbers of neurons for a structure, compared to those from age-matched control or normal rats, and the presence of gliosis or other anomalous cytomorphic pat-

terns including aggregates of dark Nissl-staining material in spaces once occupied by normal neurons [9,12].

Assessment of damage for the left and the right side of the brain was completed by the third author who did not know the treatment condition for each rat. The reliability and validity of this measurement procedure have been indicated by the strong correlations between proportion of damage scores and behavioral measures such as conditioned taste aversion [12,13], the proficiency of acquisition of an automated maze [13], and the numbers of reference or working errors for spatial memory in an Olton maze [15].

The mean of the proportion of damage within the larger, more traditional areas were then calculated by computer for the right and left side of the brain. For example the score for the mediodorsal thalamus was composed of the seven separate nuclei that compose this region [8]. All of the 32 major areas that contained some degree of neuronal loss for the left and the right sides of the brain were allowed to enter in step-wise multiple regression analyses in order to predict separately the numbers of events of boxing, biting, and mounting. Because there were only 18 brains in these analyses only three variables (brain areas) were allowed to enter each analysis.

3. Results

Fig. 1 shows the means and standard deviations for the numbers of biting episodes per hour as a function of the composition of the groups. Post-hoc analysis (Scheffe's $P<0.05$) of the statistically significant group differences [$F(6,7)=22.45$, $P<0.001$; $\eta^2=95\%$] indicated that the major source of the effect was for the groups that contained five experimental rats (and one control) or all experimental rats. These two conditions, that did not differ significantly from each other, exhibited more biting responses than did any of the other five groups including those with compositions of four experimental rats and two controls. Polynomial analysis also indicated that the relationship between the number of bites and group composition was quadratic [$F(1,7)=36.35$, $P<0.001$] and differed [$F=9.06$, $P<0.01$] from a simple linear relationship.

The means and standard deviations for the numbers of episodes of boxing per hour per rat within each cage for the different group compositions are shown in Fig. 2. One-way analysis of variance demonstrated a statistically significant group difference for boxing [$F(6,7)=9.90$, $P<0.01$, $\eta^2=90\%$]. Post-hoc analysis for the measures of

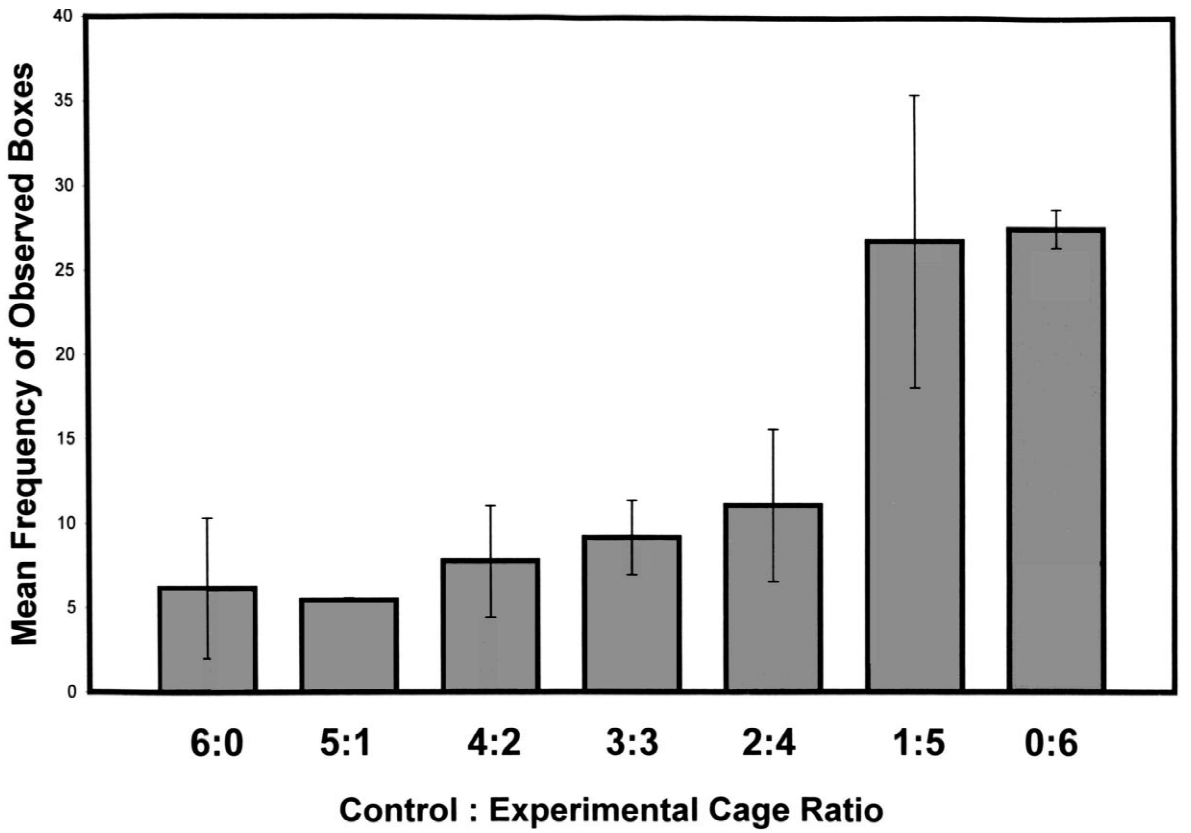

Fig. 1. Means and standard deviations (vertical bars) for the mean numbers of biting episodes per hour for groups of six rats with different compositions of controls and experimentals.

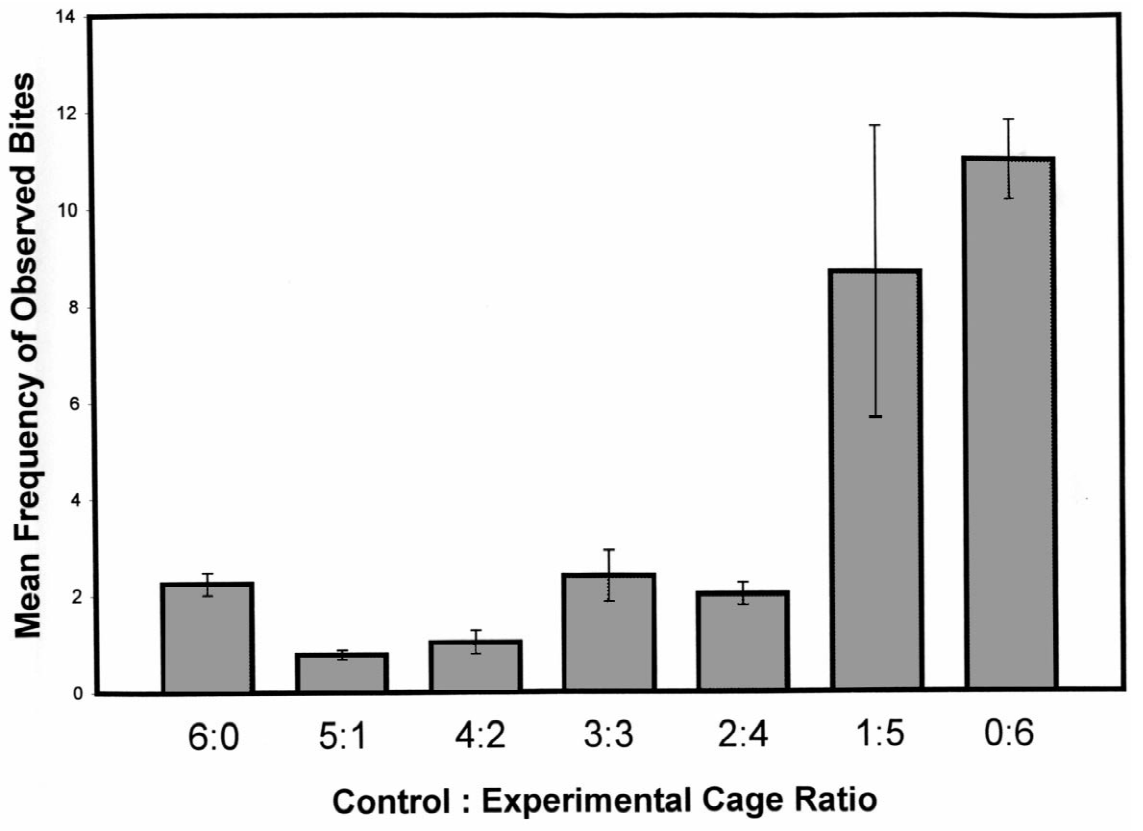

Fig. 2. Means and standard deviations (vertical bars) for the mean numbers of boxing episodes per hour for groups of rats with different compositions of controls and experimentals.

boxing indicated that the groups that contained all experimental rats or one control and five experimental rats displayed more boxing than the other groups that did not differ in a statistically significant manner from each other. Polynomial analysis for the number of boxing episodes indicated that the relationship between these episodes and the numbers of experimental rats in the group was linear [$F(1,7)=46.79$, $P<0.001$]. There were no statistically significant differences between groups for the numbers of episodes of mounting [$F(6,7)=1.28$, $P>0.05$].

To discern the separate impact of the experimental rats upon the control rats and visa versa, one-way analyses of variance were completed for the mean values of the three behavioral measures for the control rats only in each group composition and for the experimental rats only in each group composition. The means and standard deviations for boxing, biting and mounting are shown in Table 1 for only the normal rats in each group composition. The results of the post-hoc test for the control rats indicated that significant group differences for biting [$F(6,8)=15.40$, $P<0.001$] and boxing [$F=17.87$, $P<0.001$] were due primarily to the marked increase in these behaviors for the single normal rats that had been housed with five experimental rats compared to all other combinations that did not significantly differ. The significant differences between groups for mounting [$F=7.02$, $P=0.01$] were due in large part to the more frequent mounting in the compositions that contained three normal and three experimental rats.

The means and standard deviations for the numbers of episodes of bites, boxing and mounts per hour for the experimental rats only are shown in Table 2. One-way analysis of variance verified the statistically significant group compositional differences for biting [$F(6,8)=15.04$, $P<0.01$] and boxing [$F(6,8)=9.05$, $P<0.05$]. Post-hoc

Table 1
Means and standard deviations for the average numbers of episodes per rat per hour for biting, boxing and mounting for normal rats only as a function of cage composition

Numbers of experimental rats per cage	Bites		Boxing		Mounting	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
0	2.2	0.2	6.1	4.1	0.3	0.3
1	0.6	0.3	5.2	0.8	0.6	0.4
2	0.8	0.2	6.8	3.8	0.8	0.8
3	2.1	1.5	11.3	1.6	3.6	0.9*
4	1.8	0.6	9.8	1.8	1.2	0.1
5	5.9	0.7	22.5	1.1*	0.9	0.9

* $P<0.05$ from all other groups in the column.

Table 2
Means and standard deviations for the average numbers of episodes per rat per hour of biting, boxing and mounting for experimental rats only as a function of composition of cage

Numbers of normal rats per cage	Biting		Boxing		Mounting	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
5	1.6	1.5	6.3	5.1	0.1	0.1
4	1.4	1.1	9.6	2.3	3.1	4.3
3	2.6	0.5	6.9	2.6	3.7	0.8
2	2.0	0.6	11.7	5.9	1.0	1.3
1	9.2	3.5*	27.6	10.1*	0.8	0.9
0	11.0	0.8*	27.4	2.3*	4.2	4.5

* $P<0.01$ from all other groups in the column.

analysis indicated that the experimental rats in the groups that contained all experimental rats or only one control rat (five experimental rats) displayed more biting and boxing episodes relative to the other compositions that did not differ significantly from each other. There were no significant group differences for mounting.

There were several qualitative observations that were persistent throughout the study. The experimental rats that were the focus of the agonistic behaviors by other rats (including controls) exhibited conspicuous ear movements that resembled vermiculate movements. Although the agonistic rats always exhibited ocular protrusions and flattened, caudally extended ears, they were rarely bitten by the subordinate rat. The rats who were the focus of the agonistic behavior remained prone (on their backs) and immobilized, often for several min, until the dominant rat had moved about 50 cm away. Before an encounter, the agonistic rats displayed tail 'twitches' when the distance from the imminent focus of the aggression was less than 30 cm. The facial area, particularly the snout and the ears were the most frequent apparent targets for the dental contact. Occasionally, the experimental rats displayed spontaneous tail-biting of other rats. These behaviors were similar to their other gnawing behaviors rather than frank aggressive responses.

The means and standard deviations for the proportion of damage within the aggregates of structures from the right side of the brain that were evaluated microscopically are shown in Table 3. Because there were no statistically significant differences (paired *t*-tests) between the proportion of damage within a given structure from the left and right side of the brains, the data for only the right side were presented.

The results of the multiple regression analyses are shown in Table 4. The brain structures, partial regression coefficients, standard error of these coefficients, the change in r^2 and the *t*-test scores for the variables are given for the numbers of mounts, bites and boxing episodes. There was a moderately strong correlation of 0.78 between numbers of bites and numbers of boxing episodes. In order to discern which structures with neuronal damage were most associated with the variance in biting episodes not associated with boxing, the residuals for the regression between these two variables were extracted and also subjected to the multiple regression analyses. The correlations between the predicted values based upon the equations composed of the amount of damage within the first three structures to enter the analysis and the observed behaviors for biting, boxing, mounting and the residual of biting–boxing are shown in Fig. 3.

Table 3
Means and standard deviations for the proportion (percentage) of damage within the clusters of major structures affected by the seizures within the right side of the telencephalon and diencephalon

Structure	Mean	S.D.	Structure	Mean	S.D.
Entorhinal cortex	19	14	Basolateral amygdala	29	20
Subiculum	23	19	Medioamygdala	40	18
CA fields	44	26	Central amygdala	0	0
Dentate gyrus	33	32	Intercalated area	6	10
Occipital cortex	12	14	Anterior amygdala	1	5
Retrosplenial cortex	6	5	Medial geniculate	9	9
Cingulate	2	5	Posterior thalamus	18	12
Temporal cortex	34	37	Lateroposterior thalamus	47	28
Parietal cortex	45	39	Laterodorsal thalamus	74	33
Frontal cortex	12	20	Intramedullary thalamus	6	24
Insular cortex	38	33	Lateral geniculate	3	4
Orbital cortex	3	5	Habenula	0	0
Piriform cortex	56	39	Ventral thalamus	20	18
Endopiriform N.	43	40	Intralaminar thalamus	17	11
Substantia nigra	8	8*	Midline group	35	12
Caudate–putamen	9	14	Mediodorsal group	36	16
Amygdala–striatum	8	9	Anterior thalamus	8	11
Pallidum	1	2	Extended amygdala	3	7
Ventral striatum	0	0	Septum	3	4
Olfactory tub.	0	0			
Corticoamygdala	32	18			

* Only the reticulata.

Table 4
Partial regression coefficients, standard errors, *t*-scores and change in r^2 for structures (Mean and S.D. values in Table 3) that accommodated the maximum variance in numbers of events of mounting, biting, and boxing for rats ($n=18$) with histories of seizures (The data for the unique variance in biting not correlated with the boxing (the residuals) are also shown)

Variable	*B*	S.E.B.	*t*	r^2 change (%)
Mounting				
Right orbital	0.55	0.08	6.75	48
Left anterior amygdala	0.82	0.16	5.13	27
Right mediodorsal thalamus	−0.08	0.03	2.60	7
Constant=0.49				
Biting				
Right lateral dorsal thalamus	−0.09	0.02	4.07	21
Right intercalated group	0.20	0.07	2.90	15
Intralaminar group	0.12	0.05	2.37	15
Constant=0.96				
Boxing				
Right intralaminar group	−0.77	0.22	3.51	22
Left endopiriform group	0.02	0.06	2.66	21
Constant=2.43				
Biting–boxing residual				
Right hippocampus	−0.12	0.02	4.95	30
Right dentate gyrus	0.07	0.02	3.20	30
Right laterodorsal thalamus	−0.03	0.01	3.11	14
Constant=0.54				

About 75% of the variance in the numbers of mounting episodes [$F(3,15)=27.49$, $P<0.001$; S.E.E. 1.93] during the study were accommodated by the amount of damage (specific Paxinos and Watson structures, using their abbreviations, in parentheses) within the right orbital frontal cortices (Lo, VLo, Mo, Vo), left anterior amygdaloid group (AAv, AAsh, AAd, AA), and right mediodorsal group. Approximately one-third of the variance [$F(3,15)=7.10$, $P<0.01$; S.E.E.=3.04] in numbers of biting episodes were accommodated by the combination of damage within the right lateral dorsal thalamus (LDVL, LDDM), right intercalated group (I, IM, IMG) and left intralaminar group (CM, PC, CL, PF).

Only 43% of the variance in the number of boxing episodes [$F(2,16)=7.27$, $P<0.01$; S.E.E.=9.84] was associated with the combination in the proportion of damage within the right intralaminar group and the left endopiriform nuclei; only two variables met the criteria to enter the equation. About 75% of the variance in the residuals (more biting episodes than predicted by boxing episodes) from the correlation between biting and boxing was accommodated [$F(3,15)=18.28$, $P<0.001$; S.E.E.=1.26] by the combination of damage within the four CA fields within the right hippocampus, the right dentate gyrus, and the right lateral dorsal thalamus. Although there was no significant correlation between the predicted values for the numbers of mounts and numbers of bites ($r=0.24$), there were weak significant associations between the numbers of predicted boxing episodes and mounting (0.48) and the numbers of predicted bites and boxing (0.49).

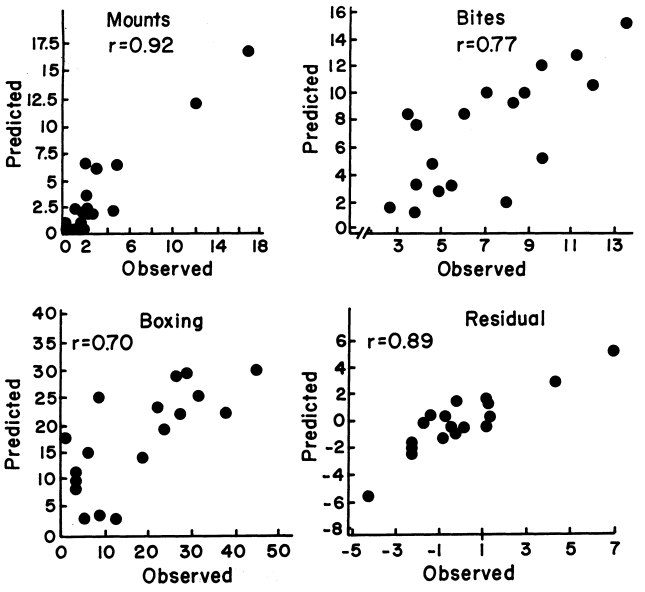

Fig. 3. Multiple *r* (correlations) values between the predicted and observed scores for the equations in Table 4 for numbers of mounts, bites, and boxing episodes. The association between residual bites (after the correlation with boxing episodes have been removed) and predicted values is also shown.

4. Discussion

The results of this study indicated that intermale agonistic behavior can be influenced by the composition of the social group. The magnitudes of the two major agonistic behaviors, biting and boxing, displayed by the experimental rats were similar to normal rats if there were at least two normal rats within the composition of the group. If only one of the six rats within the group was a normal rat, the magnitude of the intragroup agonistic behavior was not decreased from that of homogeneous groups of rats whose aggression had been increased due to the experimental treatment. Inspection of the behavior of the normal rats indicated that the single normal rats housed with groups of experimental rats were also significantly more aggressive than a normal rat housed with all normal rats or combinations of normal and experimental rats.

The functional relationship between the numbers of experimental rats and the averages for boxing and biting was not linear. Instead, a quadratic relationship was found that indicated a threshold for the display of aggressive behavior in groups of six rats housed in these conditions. That this phenomenon is an artifact of the number of rats is not likely. Our previous research [1,6] has shown that groups of four experimental rats displayed amounts of agonistic behavior, as defined by boxing and biting, that were comparable to those exhibited by groups of rats

containing all experimental animals or one normal and five experimental animals. In the present study groups of rats containing four experimental animals and two controls exhibited normal levels of agonistic behaviors.

Unlike other studies, the amount of mounting [6,11] was not systematically affected by the composition of the groups. However, the rats in this study were not physically restrained [2] after the lithium/pilocarpine seizures had been induced and the acepromazine had been injected. It is possible that the specific treatment of rats following the induction of lithium/pilocarpine seizures may affect the course of damage reflected weeks later as neuronal dropout. Unpublished data by Persinger, Peredery and Bureau have shown that 100% of 40 rats that had been either restrained for 19 h after the induction of the seizures ($n=20$) or returned to the home cage ($n=20$) could be discriminated on the bases of the linear combination of the proportions of neuronal dropout (when the brains were removed 2 months after seizure-induction) within the inner blade of the dentate gyrus, the centrolateral thalamic nucleus, anteroventral thalamic nucleus, and area 2 of the parietal cortices.

We measured the gross damage rather than the densities of neurons and glial cells within the structures listed in Table 3. Desjardins and Persinger [6] had found strong ($r>0.90$) correlations between the numbers of neurons within the central nucleus of the amygdala, a nucleus that is almost never damaged by the experimental treatment, and the amount of biting and boxing. Although the measures employed in the present study have been strongly correlated with neuronal densities within key thalamic and amygdaloid structures [9] and with the quantitative measures of more protracted behaviors such as maze learning and conditioned taste aversion, it is possible that the greater precision at the level of cell density may be required to reveal a reliable association with agonistic behaviors.

The functional significance of the proportion of damage within the specific regions of the brain that predicted the biting and boxing in this study might be explained. Neuronal activity, not the absence of neurons, produces active behaviors. Consequently the structures that entered the equations would be expected to be inhibitory for other regions or to contain interneurons that inhibit the circuitry generating these behaviors. Loss of these neurons would have disinhibited the pathways that normally modulated the aggression. That the relationship is more complex than the amount of gross damage was indicated by the entry of structures into the equations whose proportion of damage were distributed along the entire range of damage.

Desjardins and Persinger [6] had hypothesized that the marked increases in agonistic behaviors were encouraged by the disinhibition of the central nucleus from proximal nuclei within the amygdala that were significantly damaged by the consequences of the seizures. The increased damage within the intercalated amygdala that was positively associated with numbers of bites would be consistent with this interpretation in light of the axonal collaterals from this region that penetrate the central nucleus and modulate its function [5]. This conclusion assumes that these collaterals had maintained an inhibitory function over the neurons within the central amygdala and its projections to the hypothalamic regions that coordinate agonistic sequences.

The correlations between damage within the hippocampal formation, specifically the CA fields of the hippocampus and the dentate gyrus upon the residual of biting responses, not correlated with boxing, indicate that once the boxing–biting pathways have been initiated, stimulation from other sources might contribute to the persistence or the ‘perseveration’ of the biting component of the attack. That less damage within the hippocampus but more damage within the dentate gyrus was associated with more bites from a different source of variance suggests a second pathway contributes to these motor responses. The hippocampus and the amygdala are considered important components to the neural circuitry that contributes to violent behavior in many species [4,7].

Nine of the eleven structures that entered the equations for the four types of behavior involved the right side of the brain even though there were no significant differences for the proportion between the left and right side for any of the structures. These results may suggest that the electrical activity within the right hemisphere may control the expression of these behaviors. We have observed, repeatedly, that more than two-thirds of the overt spontaneous motor seizures displayed by these rats during their lifetimes begin with the left forelimbs and then generalize to bilateral forelimb myoclonus followed occasionally by tonic–clonic convulsions or the type of rapid running and jumping evoked by picrotoxin injections [14].

If this model is applicable to the present study, then social stimuli associated with the composition of the group might attenuate the release of aggressive behaviors by the experimental rats. Although olfaction would appear to be an obvious cue [5], our behavioral observations strongly suggest that the experimental rats are either anosmic or dysnosmic as defined by behavioral testing. We suggest that detailed analysis of the interactional patterns in this paradigm may show that the sign stimuli responsible for modifying intermale aggression may require the presence of only two or more normal rats.

Acknowledgements

Thanks to Chris Blomme and Lorraine Brosseau for technical assistance. The contributions of Dr William Holley, Ministry of Agriculture, Ontario concerning care of rats and suggestions for monitoring were appreciated.

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